IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1648
ZEBEDEE et al.	Examining Attorney: Zachariah Lucas
Serial No.: 10/677,956	
Filed: October 1, 2003	Date: June 19, 2008 Pasadena, California
For: METHODS AND SYSTEMS FOR PRODUCING RECOMBINANT VIRAL ANTIGENS	

REPLY BRIEF

In response to the Examiner's Answer ("Answer") dated May 12, 2008.

Since the Answer fails to clearly acknowledge what it is that Appellant has invented, we reiterate.

Generic claim 141 is to an NANBV (HCV) detection assay using the combination of the capsid antigen and C-100-3 antigen. Appellant discovered that the capsid antigen detects those antibodies associated with early seroconversion following HCV infection. At a late or chronic stage following HCV infection, the antibodies in a sample differ in that they are primarily anti-C-100 antibodies. Appellant found that these antibodies are not reliably reactive with the capsid antigen, see Substitute Specification,

page 104, Table 5, chimp 10, week 51 where there was no reaction with the capsid antigen. These results provide the unexpected result from using capsid antigen together with the C-100-3 antigen in an HCV assay. Appellant found that the capsid antigen binds to anti-capsid antibodies (not recognized by C-100 antigen), and provides for detection of HCV seroconversion at early times after infection. The C-100-3 antigen ("Anti HCV" in Table 5), detects those antibodies which the capsid antigens fail to detect, viz., those anti C-100-3 antibodies present in chronic or late HCV infection. Thus, the combination for the first time provided detection of infection over the full span of times following exposure to HCV. This provided an important breakthrough in HCV detection and it is neither inherent in nor obvious from the '671 patent.

When patients or blood donors present, there is no way of telling when they might have become infected. Hence, there is no telling the antibody type present in the blood serum. The once common failure to detect HCV infection in cases of active infection, in individuals and blood banks, sometimes referred to as "false negatives", has been greatly reduced by the present invention.

The Answer waivers between rejection on Houghton '671 under 35 U.S.C. 103(a) and "anticipation" which implicates 35 U.S.C. 102, Answer at (9), compare first sentence of the first paragraph with the final sentence of the second paragraph (appearing at page 4, top).

However, the Answer affirmatively states that Houghton '671 does not teach the combined use of the capsid antigen with the C-100-3 antigen, Answer, page 4, second paragraph. This obviates any contention of anticipation and, hence, we address the facts and the applicable law in the context of Section 103(a).

The Examiner has not made out a case of prima facie obviousness based on the '671 patent.

The Examiner first erroneously characterizes the '671 patent disclosure of capsid antigens. The Examiner then argues it would be prima facie obvious to combine compositions known in the art to perform the same function, citing MPEP 2144.06.

The capsid antigen and the C-100-3 antigen do not perform the same function. They perform different functions, contrary to the teaching of the '671 patent.

While seemingly unappreciated by the Examiner, these newly discovered functions are of critical importance in reducing the incidence of false negatives in the testing for HCV infection and provide surprising and unobvious results.

1. No Inherency/Latency Established

The Examiner incorrectly assumes that by following the teaching of the '671 patent, the capsid antigens referred to as CA 259 and CA 290 in Figure 65, inherently detected the antibodies from early detections (anti-capsid antibody). As we pointed out in our opening Brief, the antigens disclosed in the '671 patent, Figure 65 and Specification, column 83, lines 17 et. seq. (where CA 259 is apparently referred to as CA 279), were obtained by rudimentary means which do not even allow for reproducibility and the properties of antigens as described in the '671 patent show no relevant differences between CA 259/290 and C-100, contrary to Appellant's discovery of critical differences.

The Examiner's argument that a finding of a DNA-sequence automatically equates to any and all properties of the protein which corresponds to that DNA sequence is deeply flawed. The "inherency" can be established only if, and only if, the property can be demonstrated as part of an experimental design which allows an inventor to observe it and to confirm the discovery again and again, very much as was done by Appellant. Whether the '671 patent clones in the rudimentary manner Houghton prepared and used them did indeed possess these characteristics is contraindicated by the results reported in Figure 65, summarized again below. If the '671 antigens possessed the requisite properties, then he should have derived this conclusion from the data he reported in Figure 65. But, the '671 experimental data

points in the opposite direction. A claim that his capsid-related clones " inherently" were able to detect seroconversion at early times after infection is not supported anywhere in '671. Whether the reason for this failure is the result of poor assay design, or expression level of antigens of interest, or their molecular shape, or simply impurities present in the expressed clones used for the screening (which may have caused such a high background signal that it was impossible to distinguish between an authentic antigen/antibody complex formation and an artefact due, for instance, to the radioactively-labeled indicator binding to some contaminant present,) or, for yet some other reason, is, in fact, irrelevant. The unequivocal conclusion is that in the end, Houghton failed to both discern and document the critical capsid feature of early detection because it was not present in his experimental designs, and the Examiner is therefore wrong in attributing an inherent capability to a protein just by invoking, that the sequence of the DNA which encodes it, would in any way, be sufficient to disclose all of the properties of said protein.

Table 65 at the top left header refers to results in “chimps”. The “post acute” chimp serum tested negative to CA 259 and CA 290, indicating that the serum either did not contain anti-capsid antibody, or CA 259/CA 290 did not recognize it. In any event, “post acute” is ambiguous and may be understood to mean that the serum was obtained after infection and after the acute illness which developed as a consequence of said infection. The time interval separating these events is not disclosed in the ‘671 patent.

With regard to Figure 65 with the headers over the subjects 1 to 8 which state "chronic HCV patient C100 positive" and the reference to "serum from individuals" (column 83, lines 18 to 19, and more specifically in column 82, lines 64 to 68, which appear to refer to the same eight sera), it follows that all of these '671 subjects pre-tested positive for anti C 100 antibody. The "Chronic C100 positive" indicates that sera were obtained at a later stage after infection and that the CA 259 and CA 290 antigens also tested positive (in four serum samples). There is no evidence that Houghton ever investigated capsid reactivity with sera taken from patients taken at early times after infection. The '671 patent does not disclose any detection of seroconversion at early times after infection whether by capsid antigens, or by the C 100 antigen.

Since there is no evidence in '671, that Houghton had recognized any capability of his purported capsid antigens to detect seroconversion (to detect anti-capsid antibody) at early times after infection, it is also *prima facie* obvious that he could not discern any merit in combining the capsid antigen with C 100. *Res ipsa loquitur.*

The final sample in Figure 65, is identified as "Convalescent, C-100 negative" and scored as reactive with the capsid. This is not a disclosure of early detection. Other than being identified as "C-100 negative", the etiology of this specimen is not disclosed in the '671 patent. As noted in our opening Brief, the definition of "convalescence" as provided by Wikipedia is as follows:

> Convalescence is the gradual recovery of health and strength after illness....It refers to the later stage of an infectious disease when the patient recovers and returns to normal, but may continue to be a source of infection even if feeling better.

"Convalescent C-100 negative" is thus an uncertain term which implies a point in time when someone is at some stage of recovery from disease and well beyond the time of original infection. There is no suggestion in '671 that this serum originated from a specimen taken at early times after infection – indeed, "convalescent" contraindicates recent or early infection and the only reasonable inference is that it refers to a later stage of, in this case, HCV infection.

The Examiner's allegation of inherency or latency is contrary to the teaching of the '671 patent. The detection of anti-capsid antibody, an essential feature of Appellant's claims, is not inherent.

The Examiner has not provided a rationale or any evidence tending to show inherency, MPEP 2112. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re

Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Also the Board of Patent Appeals and Interferences in Ex Parte Gleave, 84 USPQ 2d 1681 (2006) which states:

> [1] It is well settled that a prior art reference may anticipate even when claim limitations are not expressly found in that reference, but are nonetheless inherent in it. *See,* e.g., *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 773 (Fed. Cir. 1985). However, it is also the case that '[i]nherency...may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.' *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

With regard to Examiner's comment regarding Figure 65, Answer, page 7, Appellant's arguments are not based on conjecture, but on the facts as presented in Figure 65, and their only logical and reasonable presentation. Figure 65 is the only evidence as to how the capsid antigens, as disclosed in '671 patent, actually performed except for the (meaningless) statement that they were "very immunogenic", column 83, line 21. However, in the search for passages in the specification which address the capsid antigens, the claim, on behalf of the CA 279 and CA 290 antigens, that these were "very immunogenic" had to be addressed as this, and Figure 65 data, are the only information on their immune reactivity which is disclosed in the '671 patent.

The above reveals the unsupported and impermissibly speculative nature of the Examiner's contention that the anti-capsid antibody and/or the reaction of capsid antigen with anti-capsid antibody, a critical feature of the method of the claims on appeal, is inherent in the '671 patent. The characteristics of the CA 279, CA290 capsid antigens --as disclosed in Houghton-- run contrary to any alleged inherent or latent feature of utility for an early detection of seroconversion. Consequently, at the very best, if these antigens **may** have had some (unrecognized) capability for the detection of early seroconversion, even such, unjustifiably liberal, and inevitably speculative interpretation, of the Houghton disclosure is insufficient to establish inherency as a matter of law.

2. No Obvious Combination

The Examiner's argument that it would have been obvious to combine capsid-antigen with C-100-3 antigen in an HCV assay, on the assumption that they provide the "same function" fails. Appellant discovered the critical difference in the function of the capsid and C-100-3 antigens in HCV infection detection. There is no suggestion in the '671 patent that any one of the theoretically dozens or even hundreds of possible antigen combinations would provide the solution to the "false negatives" hazard. The failure of Houghton to recognize critical differences in the properties of the antigens teaches away from combining them.

The two antigens, capsid and C-100-3, as combined in the present invention complement each other. The two antigens clearly do not perform the same function. It is, in fact, abundantly evident that the antigens do indeed recognize different antibodies (anti-capsid antibody recognizes an epitope on the capsid and not on the C-100-3 antigen and the anti C-100-3 antibody recognizes an epitope on the C-100-3 antigen and not on the capsid). Thus, they are not useful *for the same purpose* and MP2144.6 is irrelevant.

Furthermore, and, importantly, the discovery of the function of the capsid by Appellant provided the predicate for successfully combining the C-100-3 and capsid to achieve a major advance in anti-HCV assays as compared with a method reliant on a

single antigen. Houghton failed to note any significant advantage to be achieved by combining any antigen with the C-100-3 antigen. Thus, the '671 patent teaches away from the combination successfully employed according to Appellant's invention. Houghton noted only that a number of other antigens also, apparently, were reactive. Houghton failed to detect the unique capability of a properly manufactured capsid antigen to serve as an early marker for detecting seroconversion. Since Houghton had available to him, adequate tools for detecting this capability (well-characterized chimpanzee sera, taken at known time points after experimentally infecting the animals), one must conclude that the purported capsid antigens of Houghton was non-reactive with those antibodies appearing early in the disease cycle. If the expressed proteins, which Houghton disclosed, did have epitopes presented in such manner that antibodies produced during early seroconversion would have formed an antigen-antibody complex, he would have realized and focused on this finding. In the present case under Appeal, the inventors were successful, because they were able to synthesize a properly expressed capsid antigen and, surprisingly, they determined that the then state of the art assay which was subject to providing false negatives was superseded by combining such a capsid antigen with C-100-3.

The Examiner's contention, that (page 5, first paragraph, page 6, last paragraph, and page 7, top) that detection of *seroconversion "at early times after infection" is a latent property and does not render nonobvious an otherwise known invention* (citing MPEP 2145 II) is not supported by the properties of the two capsid antigens (CA 259

and CA 290) as disclosed in Houghton. The DNA encoding these two antigens are derived from the nucleotides encoding HCV capsid antigen; however, it does not follow that the corresponding *antigens*, as actually expressed by Houghton, *were* capable of detecting seroconversion at early times after infection, as pointed out above.

The Houghton disclosure indicates that providing a stretch of DNA did not confer the same properties to the protein encoded by said DNA in a different environment, see, e.g. Col. 52, line 65-Col 53, line 2) which discusses the enhanced antigenicity conferred on to the protein as expressed from clone 5-1-1 as compared to that of three other overlapping clones, including clone 81 which is larger than clone 5-1-1, yet exhibits a different (poorer) antigenicity (cf Figure 65). To infer from a given nucleotide sequence that an insight has been gained to discern every feature of the product obtained upon transcription and translation of that said sequence, is ludicrous.

Examiner's arguments presented in the Answer, page 11, second paragraph appear to repeat earlier arguments which also referred to MPEP 2144.6, and hence, the response has already been presented above.

The claim by the Examiner (Answer, page 10, line 7), "*The Appellant has demonstrated no synergy that results from the combination*" flies in the face of the demonstration (see Appellants' Opening Brief (page 7, line 5), "At a late or chronic stage...found that such samples do not necessarily react with the capsid antigen, see

Substitute Specification page 104, Table 5 chimp 10 week 51 where there was no reaction with the capsid antigen. These results as disclosed in the present patent application revealed for the first time the important benefit to be derived from using capsid antigen...and when used in conjunction with the C-100-3 antigen").

In response to the Answer, page 10, last paragraph: The reasonable expectation element of the obviousness rejection:

As elaborated at pages 21 to 24 in the Appellants' Opening Brief, it was not obvious to try to combine capsid and C-100-3 based on the disclosure of the '671 patent. Figure 65 provides no motivation whatsoever to combine the two antigens in order to solve the problem of detection of seroconversion at early times since all evidence presented in the '671 patent indicates that the capsid of Houghton did not react significantly different than the C-100-3 antigen. Specifically, with regard to the data presented in Figure 65 there is no evidence of early detection of seroconversion. Whether or not the capsid might fail to react with sera from chronic cases is also unclear at best and the equivocations were probably related to the characteristics of the actual capsid preparations disclosed in the '671 patent. They appear to have reflected only poorly on the genuine characteristics of the capsid antigens. It is the Examiner's arguments which are not persuasive here.

In response to the Answer, page 11, last paragraph, the inevitable conclusion is that the capsids as disclosed in the '671 patent were inadequate in revealing its proper characteristics. Houghton failed to discover the requisite properties and it is highly speculative whether he actually isolated the capsid sequences, CA 259/290, in a form which would have revealed their actual properties.

Forest Laboratories Inc. v. Ivax Pharmaceuticals Inc., 84 USPQ2d 1099 (CAFC Sept. 5, 2007), a post KSR decision, pertained to a patent (Reissue 34712) which claimed the pure (+) enantiomer of citalopram, also referred to as "escitalopram", 85 PQ2d at page 1101. The prior art disclosed a racemic mixture of the (+) and (-) enantiomers of citalopram :

> ...the court found that attempting to separate the enantiomers of citalopram based on the knowledge of one of ordinary skill in the art would have required undue experimentation and that the Smith reference was therefore not enabled.

> Next, the district court concluded that Ivax and Cipla had failed to prove by clear and convincing evidence that any of the asserted claims of the '712 patent were obvious. The court found that one of ordinary skill in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and

unpredictable task of resolving a known racemate. The court further found that a person of ordinary skill attempting to resolve racemic citalopram would have had no reasonable expectation of success for reasons similar to those discussed with respect to enablement of the Smith reference.

In affirming the district court's finding of validity, the Federal Circuit said:

> In response, Forest argues that any prima facie obviousness based on racemic citalopram was rebutted by the evidence demonstrating the difficulty of separating the enantiomers and the unexpected properties of (+)- citalopram. Forest argues that it was unexpected that all of the therapeutic benefit of citalopram would reside in the (+)- enantiomer, resulting in escitalopram having twice the potency of racemic citalopram. [emphasis added]

Similarly here. One skilled in the art, confronted with the problem of false negatives and the inability of C-100-3 to detect early infection, would have no reasonable expectation of success in solving this problem by combining any of the antigens disclosed in the '671 patent and likely would have been motivated to look elsewhere for a possible solution to the problem of false negatives.

In Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc., 86 USPQ 2d 1196 (CAFC 2008), the Federal Circuit noted that the Supreme Court in KSR stated, at page 1201, that obviousness of a combination may be found "when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp". Here, as with the prior art in Ortho-McNeil, the '671 patent did not identify or predict (or even recognize) the problem of false negatives and Houghton data in Figure 65 do not provide a reason to focus on these particular antigens. Houghton did not recognize the differences in the properties of antigens which are critical to the solution of the false negatives problem. The Examiner's focus here is the result of pure hindsight. Basically, Houghton presented a nearly infinite number of possibilities, not just a few as was the case in KSR, and Houghton did not recognize the critical differences in properties of antigens. Consequently, there was no reason to select any particular combination out of the theoretical myriad possibilities.

It was not "obvious to try" capsid plus C-100-3 since the '671 patent does not differentiate between the properties of antigens in any relevant way and, if this deficiency is ignored, then there is no rationale for any particular combination, save wholly arbitrary combinations of HCV antigens which are so numerous as to boggle the mind.

The decision of the Examiner should be reversed.

Dated: June 19, 2008

Respectfully submitted,

Joseph E. Mueth
Registration No. 20,532

100 E. Corson Street, Ste. 300
Pasadena, California 91103-3842
Telephone: (626) 584-0396
Facsimile: (626) 584-6862